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RESEARCH NOTE

Risk-factors for emerging bloodstream infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*

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ABSTRACT

Risk-factors for bloodstream infections caused by extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* were investigated using an exploratory case-double control study in which 43 cases (70% producing CTX-M enzymes) were compared with: (i) 86 patients with bacteraemia caused by non-ESBL-producing *E. coli*; and (ii) 86 hospitalised patients. Previous follow-up as an outpatient, urinary catheterisation and use of oxyimino-β-lactams or fluoroquinolones were independent risk-factors for ESBL-producing *E. coli* among patients with *E. coli* bacteraemia, and previous use of oxyimino-β-lactams or fluoroquinolones were also independent risk-factors among hospitalised patients. These findings may help in identifying patients at greater risk for bloodstream infection caused by ESBL-producing *E. coli* in endemic areas.

Keywords Bacteraemia, *Escherichia coli*, extended-spectrum β-lactamases, hospitalised patients, risk-factors

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Escherichia coli producing extended-spectrum β-lactamases (ESBLs) are an emerging cause of community and nosocomial infection, and are associated particularly with the worldwide spread of CTX-M types of ESBL [1,2]. The treatment options for patients with infections caused by these organisms are limited. As is the case with ESBL-producing *Klebsiella pneumoniae* [3], treatment with cephalosporins or fluoroquinolones of bloodstream infections caused by ESBL-producing *E. coli* is associated with a poorer prognosis than is carbapenem therapy [4]. As bacteraemia caused by *E. coli* is frequent, this could result in a significant increase in the use of carbapenems, which might contribute to further spread of carbapenem resistance. Knowledge of risk-factors for bacteraemia caused by ESBL-producing *E. coli* might help to identify patients at higher risk, who should therefore receive empirical coverage against these organisms, and could also permit the identification of potential intervention strategies. The objective of this study was therefore to investigate the risk-factors for bacteraemia caused by ESBL-producing *E. coli* in a non-epidemic situation.

A case-double control study with prospective recruitment was carried out in the Hospital Universitario Virgen Macarena, a 950-bed hospital in Sevilla, Spain that provides care for a population of 550 000. The case-patient group included all 43

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episodes of bloodstream infections caused by ESBL-producing *E. coli* that were diagnosed in this hospital between January 2001 and March 2005. Microbiological characterisation of the isolates and outcome of the case-patients have been described previously [4]; all isolates were clonally unrelated, and of 37 isolates that were characterised, 24 produced CTX-M-14, one CTX-M-9, ten SHV-12 and two SHV-4 [4].

In case-control studies that investigate the risk-factors for infections caused by resistant bacteria, the selection of controls among patients infected with the susceptible organism tends to overestimate the ORs for previous antimicrobial use [5]. Thus, the present study compared cases with two groups of controls (with two controls for each case in each group): (i) control group 1 included randomly chosen patients with bacteraemia caused by non-ESBL-producing *E. coli* who had been admitted to the same specialty as the corresponding case-patient; and (ii) control group 2 included randomly chosen patients who had been admitted to the same specialty and who had a length of a hospital stay that was at least as long as that of the corresponding case-patient before the onset of bacteraemia.

Variable data collected were age, gender, previous healthcare, type and severity of co-morbidities (using the Charlson index) [6], invasive procedures, use of antimicrobial agents in the preceding 2 months, source of bacteraemia (using CDC criteria) [7], and the presence of severe sepsis or septic shock [8]. Bloodstream infections were primarily defined as nosocomial or community-acquired [7]; community-acquired episodes were further classified as healthcare-associated or strictly community-acquired [9]. The study was approved by the local Ethical Committee.

The Mann–Whitney *U*-test and the chi-square test (or Fisher's exact test when appropriate) were used to compare continuous and categorical variables, respectively. Multivariate conditional logistic regression (STAT v.8.0; Stata Corp., College Station, TX, USA) for datasets 1:2 was used to identify independent risk-factors associated with bacteraemia caused by ESBL-producing *E. coli*. Variables that were significantly associated in the univariate analysis, and those with an epidemiological rationale, were included in the initial models, and were selected through a stepwise backward process.

In total, there were 43 cases and 86 patients in each control group. Univariate and multivariate analyses of variables associated with bacteraemia caused by ESBL-producing *E. coli* are shown in Tables 1 and 2. Considering the risk-factors identified using control group 1, six cases (14%) had none of the four risk-factors, 15 (35%) had one, and 22 (51%) had two or more. There were no differences in the presumed origin of bacteraemia among cases and controls: urinary tract in

Table 1. Univariate analysis of risk-factors for bacteraemia caused by extended-spectrum β-lactamase-producing *Escherichia coli*

	Cases (n = 43)	Control group 1 (n = 86)	OR (95% CI)	p	Control group 2 (n = 86)	OR (95% CI)	p
Male gender	30 (70%)	47 (55%)	1.9 (0.8–4.1)	0.09	50 (58%)	1.6 (0.7–3.6)	0.2
Age >65 years	27 (63%)	57 (66%)	0.8 (0.4–1.8)	0.6	44 (51%)	1.6 (0.7–3.4)	0.2
Previous follow-up as an outpatient	25 (58%)	28 (33%)	2.8 (1.3–6.1)	0.005	40 (47%)	1.5 (0.7–3.3)	0.2
Charlson index >2	27 (63%)	42 (49%)	1.7 (0.8–3.7)	0.1	31 (36%)	2.4 (1.4–6.3)	0.004
Diabetes mellitus	14 (33%)	32 (37%)	0.8 (0.3–1.7)	0.6	16 (19%)	2.1 (0.9–4.8)	0.07
Chronic renal insufficiency	6 (14%)	3 (4%)	4.4 (1.0–18.9)	0.05	3 (4%)	4.4 (1.0–18.9)	0.05
Chronic liver disease	7 (16%)	11 (13%)	1.3 (0.4–3.7)	0.5	6 (7%)	2.5 (0.8–8.2)	0.1
Neoplasia	19 (44%)	23 (27%)	2.1 (1.0–4.6)	0.04	23 (27%)	2.1 (1.0–4.6)	0.04
More than two previous UTIs	8 (19%)	13 (15%)	1.2 (0.4–3.3)	0.6	5 (6%)	3.7 (1.1–12.1)	0.03
Structural disease of the urinary or biliary tract	22 (51%)	53 (62%)	0.6 (0.3–1.3)	0.2	11 (13%)	7.1 (2.9–17.0)	<0.001
Immunosuppressive drugs	6 (14%)	6 (7%)	2.1 (0.6–7.1)	0.2	1 (1%)	13.7 (1.6–118.5)	0.006
Neutropenia (<1000 WBC/mm^3)	6 (14%)	9 (11%)	1.3 (0.4–4.1)	0.5	3 (4%)	4.4 (1.0–18.9)	0.05
Urinary catheter	14 (33%)	15 (17%)	2.2 (0.9–5.3)	0.05	11 (13%)	3.2 (1.3–8.0)	0.007
Venous catheter	20 (47%)	37 (43%)	1.1 (0.5–2.4)	0.7	23 (27%)	2.3 (1.1–5.1)	0.02
Endoscopic procedure	3 (7%)	3 (4%)	2.0 (0.4–10.7)	0.4	0	–	0.03
Surgery	18 (42%)	25 (29%)	1.7 (0.8–3.7)	0.1	13 (15%)	4.0 (1.7–9.4)	0.001
Previous use of any antimicrobial agent	31 (72%)	24 (28%)	6.6 (2.9–15.0)	<0.001	19 (22%)	9.1 (3.9–21.0)	<0.001
Previous use of aminopenicillins	11 (26%)	12 (14%)	2.1 (0.8–5.3)	0.1	8 (9%)	3.3 (1.2–9.1)	0.01
Previous use of oxyimino-β-lactams[a]	11 (26%)	8 (9%)	3.3 (1.2–9.1)	0.01	3 (4%)	9.5 (2.4–36.3)	<0.001
Previous use of fluoroquinolones	14 (33%)	6 (7%)	6.4 (2.2–18.3)	<0.001	6 (7%)	6.4 (2.2–18.3)	<0.001

[a]Oxyimino-β-lactams used were: cefuroxime (two case-patients, one patient in control group 1, no patients in control group 2); cefotaxime or ceftriaxone (8, 4 and 3); ceftazidime (1, 2 and 0); and aztreonam (0, 1 and 0).
UTI, urinary tract infection; WBC, white blood cells.

Table 2. Multivariate analysis of risk-factors for bacteraemia caused by extended-spectrum β-lactamase-producing *Escherichia coli*[a]

	Control group 1		Control group 2	
	OR (95% CI)	P	OR (95% CI)	p
Previous follow-up as an outpatient	2.7 (1.1–6.7)	0.02	–	–
Charlson index >2	–	–	3.2 (1.2–8.7)	0.01
Structural disease of the urinary or biliary tract	–	–	6.7 (2.4–18.7)	<0.001
Urinary catheter	3.9 (1.1–13.7)	0.03	–	–
Previous use of aminopenicillins	–	–	3.7 (1.0–12.7)	0.03
Previous use of oxyimino-β-lactams	3.9 (1.1–14.1)	0.03	12.3 (2.6–56.7)	0.001
Previous use of fluoroquinolones	6.2 (1.8–20.7)	0.002	5.4 (1.6–18.4)	0.006

[a]Duration of previous hospital stay was also included in the multivariate models (for community-acquired episodes, it was considered to be 0).

46% and 44%, intra-abdominal infection in 30% and 31%, respiratory tract in 5% and 8%, soft-tissue infection in 5% and 6%, and unknown in 14% and 11%, respectively (p 0.8). Similarly, there were no significant differences in the degree of clinical severity, with nine (21%) cases and 15 (17%) controls presenting with severe sepsis or septic shock (OR 1.2, 95% CI 0.4–3.1, p 0.6). Crude mortality was 21% (11 patients) among cases and 23% (21 patients) among controls (p 0.7).

Variables of interest were analysed in specific patient subgroups. Median (range) length of previous hospital stay in the 21 cases and 42 controls with nosocomial bacteraemia was 26 (4–58) and 12 (3–56) days, respectively (p 0.03). Bacteraemia was considered to be healthcare-associated in 14 (64%) of 22 cases and 20 (45%) of 44 controls with community-acquired bacteraemia (OR 1.4, 95% CI 0.5–3.5, p 0.4). In addition, three (14%) cases and one (2%) control were residents in nursing homes (OR 6.6, 95% CI 0.6–67.9, p 0.1).

Previous studies of risk-factors for bacteraemia caused by ESBL-producing organisms mostly concern nosocomial episodes caused by *K. pneumoniae* [10–14], but the clinical and molecular epidemiology, sources and predisposing factors for bacteraemia caused by ESBL-producing *E. coli* are completely different [1,2,4]. The present study revealed that follow-up as an outpatient, urinary catheterisation and previous use of oxyimino-β-lactams or fluoroquinolones were risk-factors for ESBL-producing isolates in patients with bacteraemia caused by *E. coli*. Furthermore, a previous extended hospital stay was associated with ESBL-producing isolates in patients with nosocomial bacteraemia. The fact that previous use of oxyimino-β-lactams or fluoroquinolones was also selected in multivariate analysis using randomly chosen hospitalised patients indicates that previous exposure to these antimicrobial agents are real risk-factors for bloodstream infections caused by ESBL-producing *E. coli* [5].

This investigation was a pilot study and thus has several limitations. Since the study was carried out in a single centre, the results may not be applicable in settings with a different epidemiological context. Also, the small number of cases did not allow the evaluation of risk-factors for some subgroups of patients, and might have been insufficient to detect other relevant risk-factors; this, in turn, would explain why 14% of the cases were not exposed to any of the risk-factors identified. Alternatively, as rectal colonisation with ESBL-producing *E. coli* is increasing among healthy individuals [15], it can be hypothesised that infections caused by these organisms may occur in patients without any specific risk-factors. A multicentre Spanish study is in progress with the aim of resolving these questions, but until more data are available, use of a carbapenem can be recommended for empirical treatment of sepsis potentially caused by *E. coli* in patients with the identified risk-factors in areas where ESBL-producing *E. coli* pose a particular problem.

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RESEARCH NOTE

Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)-α antagonist therapy: safe re-initiation of TNF-α blockers after appropriate anti-tuberculous treatment

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ABSTRACT

This study investigated the long-term outcome of patients with tuberculosis (TB) as a complication of tumour necrosis factor (TNF)-α blocker therapy. All TB cases (n = 21) complicating TNF-α blocker therapy from French university hospitals were collated between January 2000 and September 2002. Outcome was assessed via a postal questionnaire during September 2005. The mortality rate after 4 years was 4.8%, and one patient had relapsed and six (29%) patients had recommenced TNF-α antagonist treatment, after appropriate anti-TB therapy, without reactivation. These data support the concept that TNF-α antagonists can be restarted in TB patients provided that adequate anti-TB treatment has been completed.